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Original article

Efficacy and safety of porous hydroxyapatite/type 1 collagen composite implantation for bone regeneration: A randomized controlled study

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ABSTRACT

Background: Porous hydroxyapatite/collagen composite (HAp/Col) is a bioresorbable bone substitute composed of nano-scale HAp and porcine type 1 collagen. In this study, the efficacy and safety were assessed in comparison to commercially available porous β-tricalcium phosphate (β-TCP).

Methods: Patients with bone defects caused by benign bone tumors, fractures, or harvesting of autografts were randomly allocated for implantation of porous HAp/Col (n = 63) or porous β-TCP (n = 63). X-ray images were scored and used to evaluate the efficacy of the implantation until 24 weeks after surgery. Blood tests and observation of the surgical site were also performed to evaluate the safety of the implants. In total, 59 and 60 cases were analyzed in the porous HAp/Col and β-TCP groups, respectively.

Results: At 18 and 24 weeks after surgery, the highest grade of bone regeneration was more frequent in the porous HAp/Col group than in the porous β-TCP group ($p = 0.0004$ and 0.0254 respectively). Wilcoxon's rank sum test confirmed the superiority of porous HAp/Col from early time points onward ($p = 0.0084$, 4 w; $p = 0.0037$, 8 w; $p = 0.0030$, 12 w; $p < 0.0001$, 18 w; and $p = 0.0316$, 24 w). The incidence of adverse effects was higher in the porous HAp/Col group than in the β-TCP group. However, no serious adverse events were reported and no cases needed to drop out of the clinical trial.

Conclusions: The superiority of porous HAp/Col for bone regeneration in comparison to an established porous β-TCP was confirmed. Although the incidence of side effects associated with the porous HAp/Col implant was higher than that in the β-TCP group, no serious adverse events occurred that resulted in rejection of the implants.

1. Introduction

In the field of orthopedic surgery, bone grafting is generally used to accelerate the healing of bone defects, especially in the case of relatively large defects. Autologous bone grafts are the gold standard because of their osteogenic capability and mechanical properties. However, it is well known that harvesting of autografts is

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associated with various complications [1,2]. Allografts are used as alternatives to autografts and are free from the donor site morbidity that occurs with use of autografts. However, the osteogenic capability depends on the donor and processing method, and the risk of disease transmission cannot be completely eliminated [3,4]. Therefore, a demand exists for substitute materials, and various types of bone substitutes have been developed including sintered calcium phosphate, injectable calcium phosphate, demineralized bone matrix, and mineralized naturally derived polymers [3,4].

Hydroxyapatite/collagen composite (HAp/Col) that is synthesized by reacting porcine type 1 atelocollagen dissolved in H_3PO_4 solution with a $Ca(OH)_2$ suspension to obtain a coprecipitate is a recently developed material for bone substitutes. HAp/Col is composed of collagen fibers and HAp nanocrystals deposited on the fibers, and the nano-structure resembles that of natural bone[5]. The porous body of HAp/Col is formed through ice crystal formation, and the collagen fibers are cross-linked by thermal dehydration at 140 °C, which is far lower than the standard HAp sintering temperature. Therefore, the HAp nanocrystals do not bond to each other, and the resulting surface area is very large [6]. Previous studies using animal models confirmed the high osteoconductivity and bio-resorbability of HAp/Col [7,8]; furthermore, although the porosity of HAp/Col reduces its mechanical strength, the resulting sponge-like elasticity provides superb handling during surgery [9].

This clinical trial was conducted to evaluate the efficacy and safety of porous HAp/Col as a bone void filler in comparison with commercially available porous β-tricalcium phosphate (TCP), which is the current clinical standard in Japan [10,11].

2. Materials and methods

A multicenter, unblinded, randomized controlled, phase 3, clinical trial of porous HAp/Col (Refit®; HOYA Technosurgical Co., Tokyo, Japan) in comparison with a commercially available porous β-tricalcium phosphate bone substitute (Osferion®; Olympus Co, Tokyo, Japan) was conducted at six institutes. The porous HAp/Col was provided by HOYA Technosurgical Co., and porous β-TCP was purchased from Olympus Co. The study was approved by the institutional review board of each institution and conducted in conformity with Japanese good clinical practice (GCP) for medical devices.

2.1. Study design

From September 2006 to July 2010, 130 patients who required bone substitute implantation into bone defects smaller than 30 cm^3 caused by a benign bone tumor, fracture, or harvesting of a bone autograft were enrolled in this study. The number of cases was determined according to the following pro forma calculation: Prior to this clinical trial, a non-clinical animal study using a canine model that compared porous HAp/Col with porous β-TCP had been conducted. The proportion of cases evaluated as having undergone highly efficient regeneration, i.e., complete bone regeneration and complete resorption of the implant, in the porous β-TCP and porous HAp/Col groups was 40% and 80%, respectively (unpublished data). From this previous non-clinical trial and previous reports, and based on an assumption of reduced efficacy under actual clinical conditions, the proportion of cases with highly efficient regeneration at 24 weeks in the porous β-TCP group in the present study was predicted to be 10–40%, and the proportion of cases with highly efficient regeneration in the porous HAp/Col group was predicted to be 25–40% higher than that in the porous β-TCP group. Based on the 70% one-sided confidence limit for the proportion of highly efficient cases in the previous non-clinical study, the required number of cases in each group to detect superiority of the porous HAp/Col was calculated with a significance level of 0.05 and a power level of 0.80. The maximum case number (62 cases in each group) was the number calculated to be required to detect superiority of porous HAp/Col with a proportion of highly efficient responses of 65% in the porous HAp/Col group and 40% in the porous β-TCP group. The exclusion criteria are described in Table 1. Patients were registered at a registration center independent from the medical institutes and the manufacturers of the implants and allocated to the porous HAp/Col group or porous β-TCP group using a computer-based minimization method to match the cause of the bone defect, age of the patients, volume of the bone defect, and institute where the surgery was performed. Because the implants were easily distinguished by the surgeons, blinding was not considered and the surgeons were not prohibited from informing the patients of which implant was implanted. There were no notable changes in the protocol after the trial commenced. After the allocation, two patients from each group were excluded because three patients refused to participate in this study and one patient was found to meet the exclusion criteria. Then, in each group, 63 patients underwent implanted surgery. However, four patients from the HAp/Col group and three patients from the β-TCP group were excluded from the following analyses because of inappropriate interventions applied during the study (Fig. 1). The porous HAp/Col used in the study was in a block format ($10 \times 10 \times 10$ mm or $30 \times 20 \times 10$ mm, porosity: 95%, macropore size: 100–500 μm), whereas the porous β-TCP was in block ($10 \times 10 \times 10$ mm or $30 \times 20 \times 10$ mm, porosity: 75%, macropore size: 100–400 μm) and granular formats (granule sizes were 0.1–1.5, 1.0–3.0, 2.3–5.0, or 4.7–8.0 mm). Immediately prior to implantation, the porous HAp/Col was wetted by blood in the operative field or from other sites, or by normal saline, to soften the implants. In the β-TCP group, block-form implants were generally used except when the surgeons judged that the gaps between the block-form implants and the recipient bone were large enough to inhibit osteoconduction or the volume of the defects was too small to use the block-form implants.

2.2. Assessment of efficacy

To evaluate the efficacy of the implants, X-ray images were taken prior to and peri-surgery, and at 2, 4, 8, 12, 18, and 24 weeks after surgery. According to scoring criteria defined based on continuity with the surrounding tissue and bone regeneration and remodeling at the implantation site (Table 2), the images were scored by three raters independent from the trial institutions who were all orthopedic surgeons and experts in this field. Although no information regarding implant group assignment was given to the raters, they easily identified the implant material in each site because β-TCP was easily identified in X-ray images, whereas porous HAp/Col was hardly detectable. In each case, the score was assigned by majority rule, and when agreement could not be reached, the score was decided by discussion. On a scale of four points, cases that scored four points, three points, two points, and one to zero points were assessed as highly effective, effective, less effective, and ineffective, respectively. Computed tomography images were also taken in cases with an implantation volume greater than 10 cm^3 and used as references for scoring.

2.3. Safety assessment

Because both types of implant are biodegradable through resorption by osteoclasts, the effects of implantation on the patients was assessed. To assess the systemic effects of implantation,

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
Patients with bone defects caused by benign tumors, fractures, or harvesting of autografts
The volume of the bone defect was within 30 cm^3.Patients whose general condition was sufficiently stable for surgery
Patients who provided first-person informed consent
Patients over 20 years old
Patients who would be able to undergo scheduled examinations
Exclusion criteria
Patients administered the following drugs within three months prior to implantation:
steroids or other immunosuppressants
bisphosphonates
selective estrogen receptor modulators
immunosuppressive agents
Patients diagnosed with the following disorders:
osteomyelitis, malignant tumor,
severe diabetes, chronic kidney failure,
abnormal hormonal metabolism, or calcium metabolism
Patients with allergic responses to:
collagen, gelatin, hydroxyapatite, or β-tricalcium phosphate
Pregnant women
Patients with pathological fractures except for those caused by osteoporosis
Patients with transplantation sites with severe vascular insufficiency or neurological disorders

the blood and urine were tested before surgery, immediately after surgery, and 2, 4, 8, 12, 18 and 24 weeks after surgery. The local response at the implantation site was evaluated by observing the state of the operative wound.

2.4. Statistical analysis

The proportion of cases assessed as highly effective, i.e., with complete regeneration, at each time point was compared between the groups using the Mantel-Haenszel statistic. Wilcoxon's rank sum test was used to determine which implant achieved a higher efficacy score at each time point. In both analyses, stratified comparisons were performed to adjust for implanted volume.

3. Results

3.1. Assessment of efficacy

The data for the enrolled patients, implanted volume, and specifications of the implants are described in Table 3, and the locations of the bone defects are described in Table 4. Average implantation volume of the HAp/Col group and β-TCP group were 3.64 cm^3 and 3.77 cm^3 respectively. Except for patient sex as analyzed by Fisher's exact test ($p = 0.108$), the backgrounds of the patients and implanted volume were well matched between the groups. In the β-TCP group, to fill bone defects of various shapes, granular implants were used alone or together with block-format implants in 42 cases, and the block-format implants were cut to adjust to the defect shape in only 13 cases. In contrast to the β-TCP group, in 36 cases in the porous HAp/Col group, the implants were cut into the desired shape using a surgical knife or scissors because the sponge-like elasticity of the porous HAp/Col enabled superb handling and easy cutting (Fig. 2).

The progression of the factorial estimations and the overall efficacy scores over time as determined from x-ray images were shown in Figs. 3 and 4 respectively, and the scores at 24 weeks

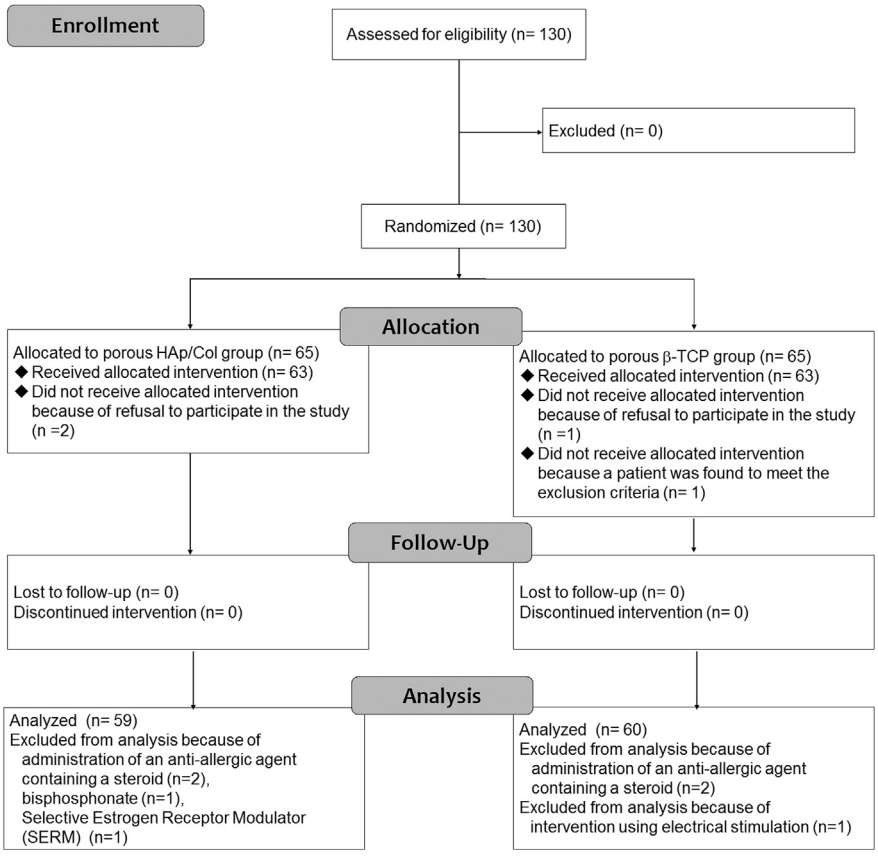

Fig. 1. CONSORT diagram showing the flow of patients in the study.

Table 2
Scoring criteria for assessing efficacy of the implants using X-ray images.

Evaluation	Score	
Evaluation of marginal zone (Osteointegration, radiolucent line)	2	All-around osteointegration
	1	Partial osteointegration
	0	All-around radiolucent line
Bone regeneration (Degradation and replacement of the implant)	2	Complete replacement by regenerated bone
	1	Partial replacement by regenerated bone
	0	No bone regeneration or no degradation of implants
	Total score	
4	Highly effective	
3	Effective	
2	Less effective	
1 or 0	Ineffective	

Table 3
Data for the enrolled patients, implanted volume, and specifications of the implants.

		P − HAp/Col	P − β-TCP
Sex (male/female)		28/31	36/24
Age (years)			
59 ≦		28	25
40 ≦ 59		25	27
20 ≦ 39		6	8
Mean (SD)		43.2 (13.4)	43.2 (14.8)
Bone defect caused by			
Bone tumor		46	48
Fracture		3	2
Harvesting of autograft		10	10
Implantation volume (cm^3)			
3		38	36
3 ≦ 10		15	17
10 ≦ 30 cm^3		6	7
Mean (SD)		3.64 (5.43)	3.87 (5.17)
Type	Size		
Block	10 × 10 × 10 mm	52	17
	30 × 20 × 10 mm	7	6
Granule	0.1–1.5 mm	–	4
	1.0–3.0 mm	–	22
	2.3–5.0 mm	–	10
	4.7–8.0 mm	–	6

sorted by implanted volume are shown in Fig. 5. In the cases with an implanted volume greater than 10 cm^3, after the scores were determined based on x-ray images, CT images were secondarily used to validate the scores. Although the scores improved over time during the follow-up period in both groups, the scores in the HAp/Col group increased earlier. At 18 weeks after surgery, 44.7% of the HAp/Col cases achieved remarkable efficacy (i.e., complete regeneration), whereas only 13.9% of the β-TCP cases showed remarkable efficacy. However, most cases in both groups were assessed as effective or better (HAp/Col: 94.7%, β-TCP: 83.3%) at 24 weeks after surgery, which was the last follow-up time point of the study.

Table 4
Location of bone defect.

	P − HAp/Col	P − β-TCP
Scaplula, clavicle, ribs	3	2
Upper extremity	31	27
Humerus	2	1
Ulna	5	1
Radius	4	4
Carpal bones	2	1
Metacarpal bones, phalanges of hand	18	20
Ilium	5	9
Lower extremity	20	22
Femur	2	5
Patella	2	1
Tibia	4	5
Fibula	1	2
Calcaneus, talus	3	1
Metatarsal bones, phalanges of foot	8	8

At each time point, the proportion of the cases assessed as highly effective was compared using the Mantel-Haenszel statistic (Table 5). At 18 and 24 weeks, the proportion of highly effective cases was significantly higher in the HAp/Col group than in the β-TCP group ($p = 0.0004$ and $p = 0.0254$, respectively). Stratified Wilcoxon's rank sum test performed at each time point indicated superiority of the porous HAp/Col from early time points onward, with $p = 0.0084$ at 4 weeks, $p = 0.0037$ at 8 weeks, $p = 0.0030$ at 12 weeks, $p < 0.0001$ at 18 weeks, and $p = 0.0316$ at 24 weeks. The effects of sex, age, and defect size on efficacy were also analyzed but determined to not be statistically significant.

3.2. Safety assessment

Adverse events that had the possibility of being associated with the implants were assessed as side effects of the implantation. The side effects that occurred in both groups are shown in Table 6. Although 18 cases among the 59 HAp/Col cases (30.5%) presented side effects, the side effects in 15 of these cases subsided without any treatment, whereas in three cases considered to be associated with infection, the side effects subsided upon antibiotic administration. Side effects were also observed in two cases in the β-TCP group (3.4%); one case resolved without treatment, and the other required antibiotic administration. Thus, the side effects in either group were not sufficiently severe to cause cases to drop out from the study. In the HAp/Col group, 2 cases indicated transient mild increase of bilirubin although the preoperative bilirubin value had also been increased in one of the cases. In two cases of the HAp/Col group, AST, ALT and γ-GTP were increased. In one of the cases (implant volume: 0.3 cm^3), the preoperative basal values of the patient had already been increased and the increase persisted at constant levels throughout the study period except for at two weeks after the surgery when the value increased transiently. In the other case (implant volume: 1 cm^3), exhibited transient mild increases around two weeks of the implantation. Four cases of the HAp/Col group exhibited mild increase of WBC after surgery. However, the value returned to normal level within a few weeks. In five cases of the HAp/Col group, CRP exhibited increase after surgery and then returned to a normal level in the same manner as WBC. All the WBC or CRP increased cases were also included in the cases of wound swelling, rubor, increased effusion or infection. The infection case of the β-TCP group exhibited increase of WBC and CRP four weeks after the implantation, and the value returned to normal level within a few weeks. Two patients in HAp/Col group

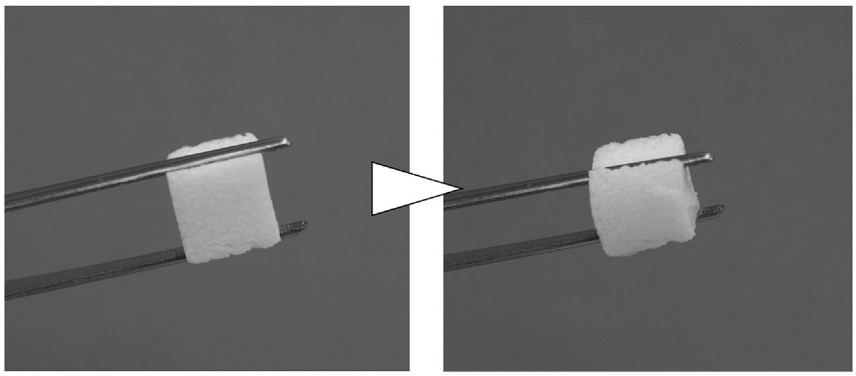

Fig. 2. Sponge-like elasticity of wet porous HAp/Col provides superior handling during surgery and facilitates cutting with a surgical knife or scissors.

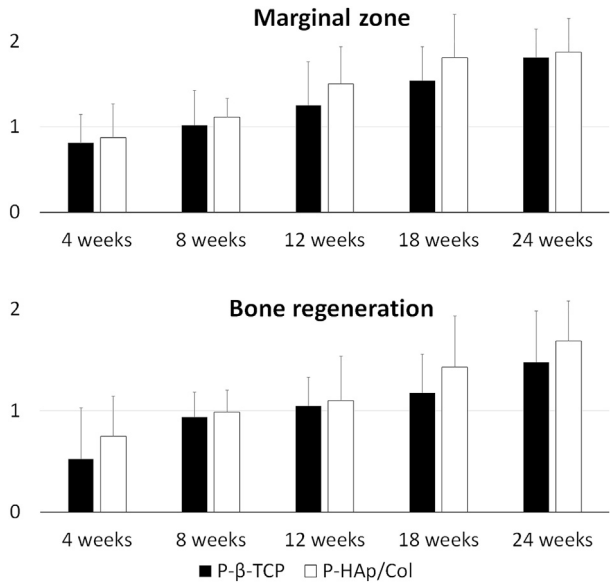

Fig. 3. The score of marginal zone was scored based on continuity with the surrounding tissue and the score of bone regeneration was scored based on bone regeneration and remodeling at the implant site.

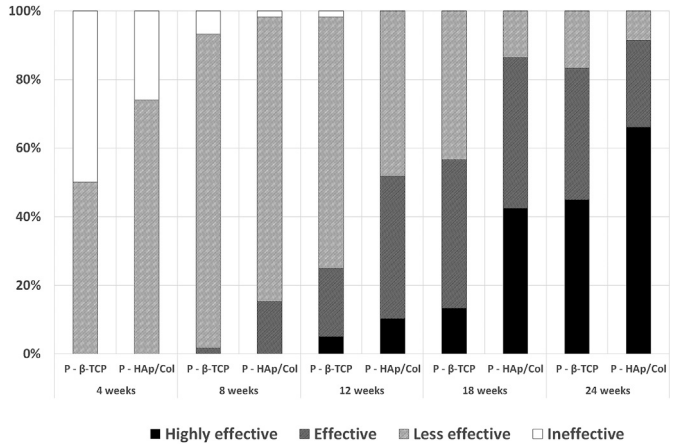

Fig. 4. Results of x-ray evaluation. The scores improved over time during the follow-up period in both groups. At each time point, the score in the HAp/Col group was higher than that in the β-TCP group.

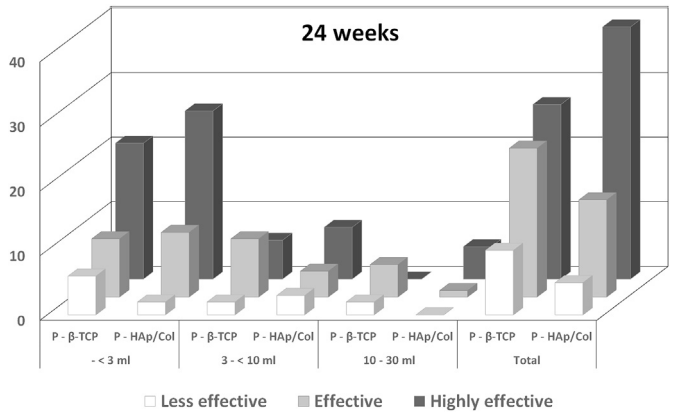

Fig. 5. Results of x-ray evaluation at the end point of the study. The case numbers assigned to each grade are presented and classified according to the implanted volume.

Table 5
Proportion of cases assessed as highly effective.

		% Of highly effective	95% Confidence interval	*P* -value
12 w	P – HAp/Col	10.3	3.9–21.2	0.2980
	P – β-TCP	5.0	1.0–13.9	
18 w	P – HAp/Col	42.4	29.6–55.9	0.0004
	P – β-TCP	13.3	5.9–24.6	
24 w	P – HAp/Col	66.1	52.6–77.9	0.0254
	P – β-TCP	45.0	32.1–58.4	

complained pain at the implant site. However, there was no relevance with wound swelling, rubor or effusion.

3.3. Case reports

Case 1: Implantation into an autograft harvest site (female, 59 years of age) (Fig. 6).

An autograft containing cortical bone was harvested from the ulnar to provide a strut bone graft for necrotic lunate. Porous HAp/Col (2 cm^3) was then implanted into the harvesting site. At 24 weeks after surgery, although obvious bone regeneration was observed, the shape of bone at the harvest site sagged compared to the original shape. Also in other cases whose implants were exposed to extraskeletal tissue due to the lack of cortical bone like the case 1, the regenerated bone sagged to some extent at the exposed aspects regardless of the implant. An efficacy score of 3

Table 6
Adverse events possibly associated with the implants.

Side effects		P − HAp/Col		P − β-TCP	
		Number	%	Number	%
Abnormal value of	ALP	1	1.7	0	0.0
	AST, ALT, or γ−GTP	2	3.4	0	0.0
	Bilirubin	2	3.4	0	0.0
	Total protein	1	1.7	0	0.0
	Ca	1	1.7	0	0.0
	P	3	5.1	1	1.7
	WBC	4	6.8	1	1.7
	CRP	5	8.5	1	1.7
Detection of urine protein		1	1.7	0	0.0
Contracture of joints		1	1.7	0	0.0
Fracture		0	0.0	1	1.7
Local warmth		1	1.7	0	0.0
Wound swelling, rubor, increased effusion		6	10.2	0	0.0
Whitish effusion		2	3.4	0	0.0
Infection of the implant site		2	3.4	1	1.7
Pain		2	3.4	0	0.0

was assigned and the regeneration was classified as effective [2 (marginal zone) + 1 (bone regeneration) = 3 (total)].

Case 2: Implantation into a bone defect caused by a benign tumor (male, 41 years of age) (Fig. 7).

Porous HAp/Col (1.75 cm^3) was implanted into a bone defect caused by enchondroma of the proximal phalanx of the thumb. Immediately after surgery, thinning of the cortical bone and disappearance of the trabecular bone was observed. At 24 weeks after implantation, recovery of cortical bone thickness and trabecular structure was confirmed. The final efficacy score was 4 and the regeneration was classified as highly effective [(2 (marginal zone) + 2 (bone regeneration) = 4 (total)].

Case 3: Implantation into a bone defect caused by a benign tumor (Female, 33 years of age) (Fig. 8).

Porous HAp/Col (8 cm^3) was implanted after the resection and curettage of a benign tumor of the patella. Bone regeneration at the implant site progressed with time. Although the osteosclerotic wall formed by the tumor remained, adequate bone regeneration at the defect was confirmed at 24 weeks after surgery. The final efficacy score was 4 and the regeneration was classified as highly effective [2 (marginal zone) + 2 (bone regeneration) = 4 (total)].

4. Discussion

HAp/Col is composed of nano-scale hydroxyapatite (80 w/w %) and porcine skin-derived atelocollagen (20 w/w %), and its nano-structure resembles that of natural bone [5]. The porous body of HAp/Col, once wetted, becomes elastic like a sponge and is thus easy to implant into bone defects of various shapes. Animal studies have shown vigorous bone formation at sites implanted with porous HAp/Col together with bio-resorbability of the implants [7,8]. In the present study, a multicenter randomized controlled trial was conducted to confirm the clinical efficacy and safety of the porous HAp/Col. In this study, commercially available porous β-TCP was used as the control implant because it is one of the most popular bio-resorbable bone void filler materials in Japan and thus represents a clinical standard [10,11]. The efficacy scores for bone regeneration and implant resorption for porous HAp/Col increased earlier than those of porous β-TCP and thus demonstrated the superiority of porous HAp/Col. Regarding safety, although adverse events occurred more frequently in the HAp/Col group, serious adverse events did not occur and no cases dropped out.

Recently, micro-porous structures in which cells cannot migrate have been emphasized because of the importance of such structures for biomaterial osteoinductivity and osteoconductivity [12,13]. One of the key functions of the micro-pores is to increase the bioactive surface area of the material, thereby enhancing its ability to engage in biological reactions that mediate osteogenesis. The porous β-TCP used as the control in this study has a micro-porous structure with superior osteoconductivity compared to the former generation of porous HAp [11] but also limited osteoinductivity [14]. The porous HAp/Col evaluated clinically for the first time in this study also has a micro-porous structure, and the micro-pores and HAp nano-crystals of the porous HAp/Col give rise to a large surface area of approximately 70–80 m^2/g [6]. This increased bioactive area is thus considered to underlie the superior osteoconductivity of HAp/Col.

The elasticity of the porous HAp/Col is considered to be another factor contributing to the superiority of HAp/Col for bone regeneration and remodeling. Our unpublished previous study using porous HAp/Col and block-format porous β-TCP identified a difference in the osteoconduction of the implants, where gaps between the recipient bone and the implanted β-TCP block were

Fig. 6. Case 1: Implantation into an autograft harvest site. Porous HAp/Col (2 cm^3) was implanted into an autograft harvest site in the ulna. The efficacy score at the end point of the study (24 weeks) was 3 and the regeneration was classified as effective.

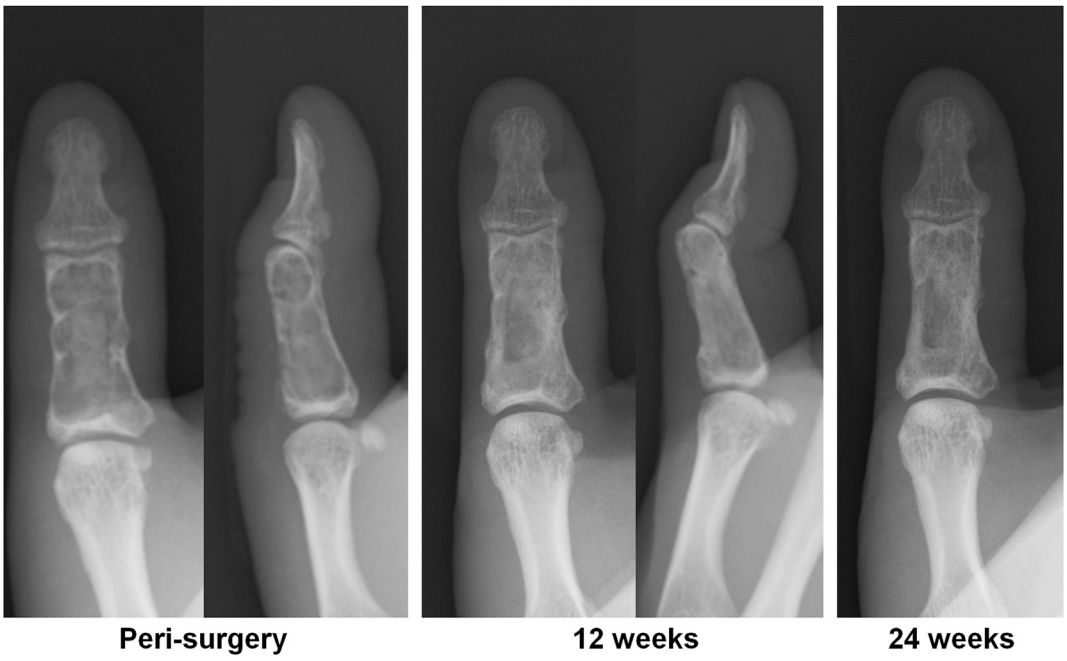

Fig. 7. Case 2: Implantation into a bone defect caused by enchondroma. Porous HAp/Col (1.75 cm^3) was implanted into a bone defect in the proximal phalanx of the thumb. The final efficacy score was 4 and the regeneration was classified as highly effective.

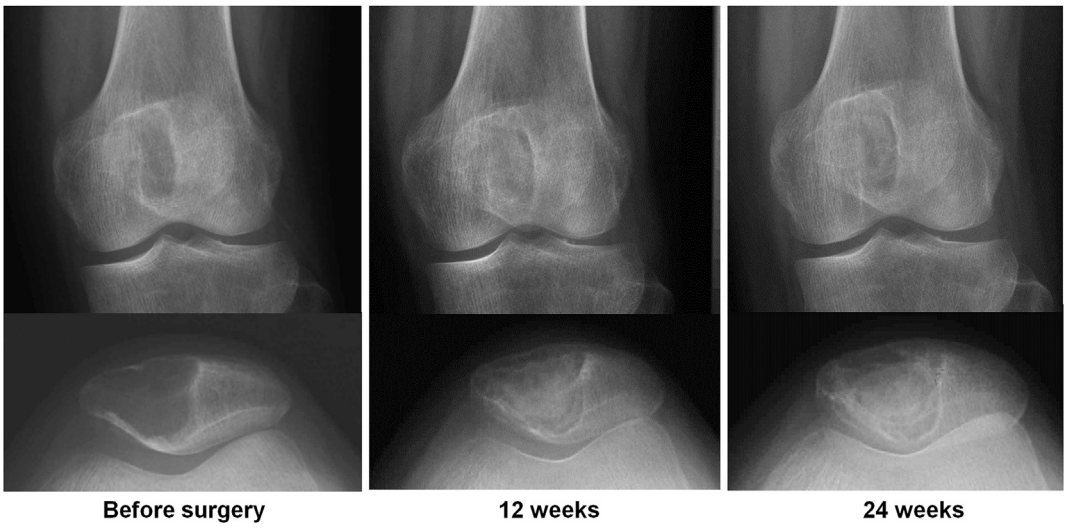

Fig. 8. Case 3: Implantation into a bone defect caused by a benign tumor. Porous HAp/Col (8 cm^3) was implanted into a bone defect in the patella. Although the osteosclerotic wall remained, the final efficacy score was 4 and the regeneration was classified as highly effective.

inevitable. Therefore, with porous β-TCP, osteoconduction from the host bone skipped these gaps, and fibrous tissue formed between the host bone and the bone that formed inside the implant. This finding corresponded with the results of a previous study that reported a radiolucent zone between the implanted porous β-TCP and the surrounding bone [11,15]. In the present study, in contrast to the β-TCP blocks, the implanted porous HAp/Col conformed to the shape of the bone defect without gaps, and the bone conduction directly progressed continuously from the host bone into the implant. Therefore, the elasticity of porous HAp/Col contributes not only to handling during surgery but also to early bone regeneration.

We used x-ray images to score the bone regeneration and remodeling. Porous HAp/Col is scarcely detectable by x-ray immediately after implantation because of its high porosity [8]. Therefore, once bone formation occurs, the newly formed bone is easily detected by x-ray, and the actual bone formation should correlate well with the x-ray findings. In contrast to porous HAp/Col, because β-TCP is radiopaque, it was difficult to detect early bone formation inside or around the β-TCP implants. Moreover, the resorption of β-TCP was slower than that of porous HAp/Col because of its lower porosity. Based on these aspects, the scoring system used in the present study may have been somewhat biased against β-TCP, especially during the early phase. In fact, the efficacy score of the HAp/Col group at 4 weeks was higher than that

of the β-TCP group, and the disaggregative results indicated the score of "bone regeneration" component of the HAp/Col group was higher than that of the β-TCP group in contrast to the equivalence of the "marginal zone" component. Therefore, the higher score of the HAp/Col group at 4 weeks would owe to these biases by the differences in sensitivity for detecting newly formed bone. In addition, the effects of these biases against β-TCP might persist until the end of the study and lower the results of the β-TCP group especially in the cases with use of large volume of β-TCP because of the slower absorption rate of β-TCP. However, at time points after the observation period of the study such as one year or two years after surgery, some β-TCP cases showed osteolytic changes of the implanted sites because of indolent resorption of the β-TCP remnants. It is therefore possible that in some β-TCP cases, the remnants were misidentified as regenerated bone, thereby artificially increasing the scores in the β-TCP group at the end point of the study. Furthermore, from a clinical perspective, it was difficult to distinguish the delayed resorption of the implant remnants from tumor recurrence. Therefore, the scores of the β-TCP transplanted cases at later stages tended to be biased to be both better and worse. These aspects may represent fundamental limitations of the scoring system based on x-ray images used in the present study especially for the β-TCP group, and at the same time, superiority of porous HAp/Col in daily clinical practice to evaluate the bone regeneration at the transplanted site.

The safety assessment revealed a higher incidence of side effects associated with porous HAp/Col implantation relative to the porous β-TCP group. The most frequent side effects were wound swelling, rubor, and increased effusion (9.5%), which were considered to be associated with a foreign body reaction, allergic reaction to HAp/Col, infection, or other inflammatory response. However, all of the side effects became asymptomatic during the study period and never required exenteration of the implant; furthermore, the side effects did not necessarily degrade the clinical results, although all cases with side effects were not presented in the results section. Therefore, serious adverse effects when using porous HAp/Col should be avoidable in the clinic by careful observation and appropriate treatment of the implant site.

The present study demonstrated that porous HAp/Col has a higher capacity for regenerating bone than a currently popular, gold standard bone substitute. However, most of the bone defects in the present study were caused by bone tumors or harvesting of autografts, and we did not evaluate the efficacy of porous HAp/Col for spinal fusion, bone defects larger than 30 cm^3, and osteochondral defects. Therefore, the use of porous HAp/Col should be validated for such applications.

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Conflict of interest

The first author receives royalty fee. The operating cost of the department to which the author belongs has been partially provided by HOYA Technosurgical Co.

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